

SEQUENCE LISTING

<110> Tang, Jordan J.N.
Hong, Lin
Ghosh, Arun K.

<120> Inhibitors of Memapsin 2 and Use Thereof

<130> OMRF 182

<140> Not Yet Assigned
<141> 2000-06-27

<150> 60/141,363
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<151> 2000-01-25

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<151> 2000-01-27

<150> 60/210,292
<151> 2000-06-08

<160> 31

<170> PatentIn Ver. 2.1

<210> 1
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<213> Homo sapiens

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cccgcccgga gggcagctt tgtggagatg gtggacaacc tgagggcaa gtcggggcag 180
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aaaaaaaaaa aa

3252

<211> 488
<212> PRT
<213> Homo sapiens

<220>
<223> Purified Memapsin 2

<220>
<223> Amino Acids 28-48 are remnant putative propeptide residues

<220>
<223> Amino Acids 58-61, 78, 80, 82-83, 116, 118-121, 156, 166, 174, 246, 274, 276, 278-281, 283, and 376-377 are residues in contact with the OM99-2 inhibitor

<220>
<223> Amino acids 54-57, 61-68, 73-80, 86-89, 109-111, 113-118, 123-134, 143-154, 165-168, 198-202, and 220-224 are N-lobe Beta Strands

<220>
<223> Amino Acids 184-191 and 210-217 are N-lobe Helices

<220>
<223> Amino acids 237-240, 247-249, 251-256, 259-260, 273-275, 282-285, 316-318, 331-336, 342-348, 354-357, 366-370, 372-375, 380-383, 390-395, 400-405, and 418-420 are C-lobe Beta Strands

<220>
<223> Amino Acids 286-299, 307-310, 350-353, 384-387, and 427-431 are C-lobe Helices

<400> 2

Ala	Gly	Val	Leu	Pro	Ala	His	Gly	Thr	Gln	His	Gly	Ile	Arg	Leu	Pro
1															15

Leu Arg Ser Gly Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg

20														30
----	--	--	--	--	--	--	--	--	--	--	--	--	--	----

Glu Thr Asp Glu Glu Pro Glu Glu Pro Gly Arg Arg Gly Ser Phe Val

35													45
----	--	--	--	--	--	--	--	--	--	--	--	--	----

Glu Met Val Asp Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val

50													60
----	--	--	--	--	--	--	--	--	--	--	--	--	----

Glu	Met	Thr	Val	Gly	Ser	Pro	Pro	Gln	Thr	Leu	Asn	Ile	Leu	Val	Asp
65															80
	70														75
Thr	Gly	Ser	Ser	Asn	Phe	Ala	Val	Gly	Ala	Ala	Pro	His	Pro	Phe	Leu
															95
85															90
His	Arg	Tyr	Tyr	Gln	Arg	Gln	Leu	Ser	Ser	Thr	Tyr	Arg	Asp	Leu	Arg
															110
100															105
Lys	Gly	Val	Tyr	Val	Pro	Tyr	Thr	Gln	Gly	Lys	Trp	Glu	Gly	Glu	Leu
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115															120
Gly	Thr	Asp	Leu	Val	Ser	Ile	Pro	His	Gly	Pro	Asn	Val	Thr	Val	Arg
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130															135
Ala	Asn	Ile	Ala	Ala	Ile	Thr	Glu	Ser	Asp	Lys	Phe	Phe	Ile	Asn	Gly
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145															155
Ser	Asn	Trp	Glu	Gly	Ile	Leu	Gly	Leu	Ala	Tyr	Ala	Glu	Ile	Ala	Arg
															175
165															170
Pro	Asp	Asp	Ser	Leu	Glu	Pro	Phe	Phe	Asp	Ser	Leu	Val	Lys	Gln	Thr
															190
180															185
His	Val	Pro	Asn	Leu	Phe	Ser	Leu	Gln	Leu	Cys	Gly	Ala	Gly	Phe	Pro
															205
195															200
Leu	Asn	Gln	Ser	Glu	Val	Leu	Ala	Ser	Val	Gly	Gly	Ser	Met	Ile	Ile
															220
210															215
Gly	Gly	Ile	Asp	His	Ser	Leu	Tyr	Thr	Gly	Ser	Leu	Trp	Tyr	Thr	Pro
															240
225															230
Ile	Arg	Arg	Glu	Trp	Tyr	Tyr	Glu	Val	Ile	Ile	Val	Arg	Val	Glu	Ile
															255
245															250
Asn	Gly	Gln	Asp	Leu	Lys	Met	Asp	Cys	Lys	Glu	Tyr	Asn	Tyr	Asp	Lys
															270
260															265
Ser	Ile	Val	Asp	Ser	Gly	Thr	Thr	Asn	Leu	Arg	Leu	Pro	Lys	Lys	Val
															285
275															280
Phe	Glu	Ala	Ala	Val	Lys	Ser	Ile	Lys	Ala	Ala	Ser	Ser	Thr	Glu	Lys
															300
290															295
Phe	Pro	Asp	Gly	Phe	Trp	Leu	Gly	Glu	Gln	Leu	Val	Cys	Trp	Gln	Ala
															320
305															310
															315

Gly Thr Thr Pro Trp Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met
325 330 335

Gly Glu Val Thr Asn Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln
340 345 350

Tyr Leu Arg Pro Val Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr
355 360 365

Lys Phe Ala Ile Ser Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val
370 375 380

Ile Met Glu Gly Phe Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile
385 390 395 400

Gly Phe Ala Val Ser Ala Cys His Val His Asp Glu Phe Arg Thr Ala
405 410 415

Ala Val Glu Gly Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr
420 425 430

Asn Ile Pro Gln Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val
435 440 445

Met Ala Ala Ile Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val
450 455 460

Cys Gln Trp Arg Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe
465 470 475 480

Ala Asp Asp Ile Ser Leu Leu Lys
485

<210> 3

<211> 503

<212> PRT

<213> Homo sapiens

<220>

<223> Pro-memapsin 2

<220>

<223> Amino Acids 1-15 are vector-derived residues

<220>

<223> Amino Acids 16-64 are a putative pro peptide

<220>

<223> Amino Acids 1-13 are the T7 promoter

<220>

<223> Amino Acids 16-456 are Pro-memapsin 2-T1

<220>

<223> Amino Acids 16-421 are Promemapsin 2-T2

<400> 3

Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly Arg Gly Ser Met Ala

1

5

10

15

Gly Val Leu Pro Ala His Gly Thr Gln His Gly Ile Arg Leu Pro Leu

20

25

30

Arg Ser Gly Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg Glu

35

40

45

Thr Asp Glu Glu Pro Glu Glu Pro Gly Arg Arg Gly Ser Phe Val Glu

50

55

60

Met Val Asp Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val Glu

65

70

75

80

Met Thr Val Gly Ser Pro Pro Gln Thr Leu Asn Ile Leu Val Asp Thr

85

90

95

Gly Ser Ser Asn Phe Ala Val Gly Ala Ala Pro His Pro Phe Leu His

100

105

110

Arg Tyr Tyr Gln Arg Gln Leu Ser Ser Thr Tyr Arg Asp Leu Arg Lys

115

120

125

Gly Val Tyr Val Pro Tyr Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly

130

135

140

Thr Asp Leu Val Ser Ile Pro His Gly Pro Asn Val Thr Val Arg Ala

145

150

155

160

Asn Ile Ala Ala Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser

165

170

175

Asn Trp Glu Gly Ile Leu Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro

180

185

190

Asp Asp Ser Leu Glu Pro Phe Phe Asp Ser Leu Val Lys Gln Thr His

195

200

205

Val Pro Asn Leu Phe Ser Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu
210 215 220

Asn Gln Ser Glu Val Leu Ala Ser Val Gly Gly Ser Met Ile Ile Gly
225 230 235 240

Gly Ile Asp His Ser Leu Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile
245 250 255

Arg Arg Glu Trp Tyr Tyr Glu Val Ile Ile Val Arg Val Glu Ile Asn
260 265 270

Gly Gln Asp Leu Lys Met Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser
275 280 285

Ile Val Asp Ser Gly Thr Thr Asn Leu Arg Leu Pro Lys Lys Val Phe
290 295 300

Glu Ala Ala Val Lys Ser Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe
305 310 315 320

Pro Asp Gly Phe Trp Leu Gly Glu Gln Leu Val Cys Trp Gln Ala Gly
325 330 335

Thr Thr Pro Trp Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met Gly
340 345 350

Glu Val Thr Asn Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr
355 360 365

Leu Arg Pro Val Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys
370 375 380

Phe Ala Ile Ser Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val Ile
385 390 395 400

Met Glu Gly Phe Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile Gly
405 410 415

Phe Ala Val Ser Ala Cys His Val His Asp Glu Phe Arg Thr Ala Ala
420 425 430

Val Glu Gly Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr Asn
435 440 445

Ile Pro Gln Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val Met
450 455 460

Ala Ala Ile Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val Cys
465 470 475 480

Gln Trp Arg Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe Ala
485 490 495

Asp Asp Ile Ser Leu Leu Lys
500

<210> 4
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 4
Ser Glu Val Lys Met Asp Ala Glu Phe Arg
1 5 10

<210> 5
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Peptide

<400> 5
Ser Glu Val Asn Leu Asp Ala Glu Phe Arg
1 5 10

<210> 6
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Peptide

<400> 6

Ser Val Asn Met Ala Glu Gly Asp
1 5

<210> 7
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Peptide

<400> 7
Lys Gly Gly Val Val Ile Ala Thr Val Ile Val Lys
1 5 10

<210> 8
<211> 4
<212> PRT
<213> Homo sapiens

<400> 8
Asp Thr Ser Gly
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<210> 9
<211> 8
<212> PRT
<213> Homo sapiens

<400> 9
Leu Val Asn Met Ala Glu Gly Asp
1 5

<210> 10
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 10
ggtaagcata cccatggcc ccaacgtc

<210> 11
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 11
gacgttgggg ccatggggga tgcttacc

28

<210> 12
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 12
acgttgtctt tgatcgggcc cgaaaacgaa ttgg

34

<210> 13
<211> 33
<212> DNA
<213> Artificial Sequence

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<223> Description of Artificial Sequence: Primer

<400> 13
ccaaattcggtt ttcggggcccg atcaaagaca acg

33

<210> 14
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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 14
ccatcctaattt acgactcactt ataggc

27

<210> 15
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 15
actcaactata gggctcgagc ggc 23

<210> 16
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 16
ctttttagca agttcagcct gtttaa 26

<210> 17
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 17
gagggtggctt atgagtatcc cttccagggt a 31

<210> 18
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 18
tggcgacgac tcctggagcc cg 22

<210> 19
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 19
tgacaccaga ccaactggta atgg 24

<210> 20
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 20
catatggcgg gagtgctgcc tgcccac 27

<210> 21
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 21
ggatcctcac ttcagcaggg agatgtcatc agcaaagt 38

<210> 22
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Oxidized
Insulin B-chain

<220>

<223> Xaa at site 3 represents cysteic acid

<400> 22

His Leu Xaa Gly Ser His Leu Val
1 5

<210> 23

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Oxidized
Insulin B-chain

<220>

<223> Xaa at site 1 represents cysteic acid

<400> 23

Xaa Gly Glu Arg Gly Phe Phe Tyr
1 5

<210> 24

<211> 5

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic
Peptide

<400> 24

Val Gly Ser Gly Val
1 5

<210> 25

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Peptide

<400> 25

Val Gly Ser Gly Val Leu Leu
1 5

<210> 26
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Peptide

<400> 26
Gly Val Leu Leu Ser Arg Lys
1 5

<210> 27
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Inhibitors

<400> 27
Val Asn Leu Ala Ala Glu Phe
1 5

<210> 28
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Inhibitors

<400> 28
Glu Val Asn Leu Ala Ala Glu Phe
1 5

<210> 29
<211> 4
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic Peptide

<400> 29
Asn Leu Ala Ala
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<210> 30
<211> 10
<212> PRT
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<220>
<223> Description of Artificial Sequence: Synthetic Peptide

<400> 30
Val Gly Ser Gly Val Leu Leu Ser Arg Lys
1 5 10

<210> 31
<211> 326
<212> PRT
<213> Homo sapiens

<220>
<223> Amino acids 2-5, 6-9, 13-20, 25-32, 65-67, 69-74, 79-87, 89-91, 99-106, 119-122, 150-154, 164-167, 180-183, 191-194, 196-199, 201-204, 210-214, 221-223, 258-262, 265-269, and 275-278 are Beta Strands

<220>
<223> Amino acids 281-284, 286-288, 298-301, 310-315, and 319-324 are Beta strands

<220>
<223> Amino acids 48-51, 111-114, 136-142, 225-234, 249-254, 271-274, and 303-306 are Helices

<220>
<223> Amino acids 12-13, 30, 32, 34-35, 73-77, 111, 117, 120, 189, 213, 215, 217-220, 287, 289, 291, 298, and 300 are residues in contact with pepstatin.

<220>

<223> Pepsin

<400> 31

Val Asp Glu Gln Pro Leu Glu Asn Tyr Leu Asp Met Glu Tyr Phe Gly
1 5 10 15

Thr Ile Gly Ile Gly Thr Pro Ala Gln Asp Phe Thr Val Val Phe Asp
20 25 30

Thr Gly Ser Ser Asn Leu Trp Val Pro Ser Val Tyr Cys Ser Ser Leu
35 40 45

Ala Cys Thr Asn His Asn Arg Phe Asn Pro Glu Asp Ser Ser Thr Tyr
50 55 60

Gln Ser Thr Ser Glu Thr Val Ser Ile Thr Tyr Gly Thr Gly Ser Met
65 70 75 80

Thr Gly Ile Leu Gly Tyr Asp Thr Val Gln Val Gly Gly Ile Ser Asp
85 90 95

Thr Asn Gln Ile Phe Gly Leu Ser Glu Thr Glu Pro Gly Ser Phe Leu
100 105 110

Tyr Tyr Ala Pro Phe Asp Gly Ile Leu Gly Leu Ala Tyr Pro Ser Ile
115 120 125

Ser Ser Ser Gly Ala Thr Pro Val Phe Asp Asn Ile Trp Asn Gln Gly
130 135 140

Leu Val Ser Gln Asp Leu Phe Ser Val Tyr Leu Ser Ala Asp Asp Gln
145 150 155 160

Ser Gly Ser Val Val Ile Phe Gly Gly Ile Asp Ser Ser Tyr Tyr Thr
165 170 175

Gly Ser Leu Asn Trp Val Pro Val Thr Val Glu Gly Tyr Trp Gln Ile
180 185 190

Thr Val Asp Ser Ile Thr Met Asn Gly Glu Ala Ile Ala Cys Ala Glu
195 200 205

Gly Cys Gln Ala Ile Val Asp Thr Gly Thr Ser Leu Leu Thr Gly Pro
210 215 220

Thr Ser Pro Ile Ala Asn Ile Gln Ser Asp Ile Gly Ala Ser Glu Asn

225	230	235	240
Ser Asp Gly Asp Met Val Val Ser Cys Ser Ala Ile Ser Ser Leu Pro			
245	250	255	
Asp Ile Val Phe Thr Ile Asn Gly Val Gln Tyr Pro Val Pro Pro Ser			
260	265	270	
Ala Tyr Ile Leu Gln Ser Glu Gly Ser Cys Ile Ser Gly Phe Gln Gly			
275	280	285	
Met Asn Leu Pro Thr Glu Ser Gly Glu Leu Trp Ile Leu Gly Asp Val			
290	295	300	
Phe Ile Arg Gln Tyr Phe Thr Val Phe Asp Arg Ala Asn Asn Gln Val			
305	310	315	320
Gly Leu Ala Pro Val Ala			
	325		